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(19)

(54) PHARMACEUTICAL COMPOSITIONS FOR INHALATION

(71) We, FISONS LIMITED, a British Company, of Fison House, 9 Grosvenor Street, London, W.1. do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a pharmaceutical powder composition for inhalation.

It is known that powder compositions may be administered by inhalation, using a device such as is described in British Patent Specification No. 1,122,284. An example of such a form of device is one which comprises a hollow elongate housing having at both ends thereof one or more passageways adapted to permit the passage of air and having one end thereof adapted for insertion into the mouth and a propeller-like device rotatably mounted in the said housing on a rigid shaft mounted in said housing and co-axial with the longitudinal axis of the housing; said propeller-like device, having on the part thereof furthest from the end of the housing adapted for insertion into the mouth, mounting means adapted to receive a container, such as a gelatine or like capsule for the medicament to be inhaled.

Medicaments for administration by inhalation should be of a controlled particle size in order to achieve maximum penetration into the lungs; a suitable particle size range being 0.01 to 10, preferably 1 to 10 microns. However powders in this particle size range are not in general readily fluidised by the above technique because of cohesive forces between the individual particles. A means of overcoming this problem is described in British Patent Specification No. 1,242,211.

According to our invention there is provided a pharmaceutical powder composition, which comprises a mixture of a solid inhalation medicament having an effective particle size, as hereinafter defined, in the range 0.01 to 10 microns and a solid carrier acceptable in the lungs, having an effective particle size, as hereinafter defined, in the range of from 80 to 150 microns.

For the purpose of the present invention there is no distinction between a single particle of given size and an agglomerate of the same size which is composed of finer individual particles. The term 'effective particle size' is therefore used herein, where the context permits, to denote the apparent particle size of a body without distinction as to the number of individual particles which go to make up that body. The effective particle sizes quoted herein for the fine particles of medicament are those as measured with a Coulter counter and those for the coarse material are as measured by sieve analysis (sieving method BS 1796).

In measuring particle sizes with a Coulter counter, the sample to be analysed is dispersed in an electrolyte into which dips a glass tube. The glass tube has a hole through the wall thereof with electrodes mounted on either side of the hole in the tube wall. The tube is immersed sufficiently for the hole and electrodes to be submerged in the liquid. The suspension is made to flow through the hole in the glass tube and as each particle passes through the orifice it displaces its own volume of electrolyte, thus changing the resistance across the hole. The change in resistance is converted into a voltage pulse with an amplitude proportional to the particle volume. The pulses are fed to an electronic counter with an adjustable threshold level such that all pulses above the threshold are counted. By setting the threshold level at different values it is possible to determine the number of particles falling within given size range and thus the proportion of particles in a sample which fall outside a desired particle size range.

The composition may contain any of a wide variety of medicaments suitable for administration by inhalation e.g. medicaments intended for alleviation of disorders of the bronchial tract or medicaments administered for systemic action. Particular examples of medicaments which may be employed in the composition of the invention are antianaphy-

lactic agents such as the di-sodium salt of 5,5' - [[5,5' - (2 - hydroxytrimethylene) dioxy]bis[4 - oxo - 4H - 1 - benzopyran - 2 - yl]] tetrazole and sodium cromoglycate, i.e. the di-sodium salt of 1,3 - bis(2 - carboxy - chromon - 5 - yloxy) - propan - 2 - ol, bronchodilators such as isoprenaline, ephedrine, adrenaline or theophylline, antibiotics such as tetracycline, steroids, enzymes, vitamins, antihistamines, mucolytics such as N-acetyl cysteine or its salts, diagnostic agents such as propyliodone or tantalum, and analgesics such as paracetamol. The composition may contain more than one medicament in finely divided form. Thus, a composition may contain for example, a mixture of sodium cromoglycate and isoprenaline sulphate. As stated above, the medicament should be in finely divided form having an effective particle size in the range 0.01—10, preferably 1—10 microns, and suitably at least 50% by weight of the finely divided medicament is in the effective particle size range 2—6 microns. Where the medicament is one of high specific activity, it may be desirable to dilute the medicament with an inert diluent of similar particle size. Such a composition should, of course, also contain a coarser carrier having an effective particle size in the range 80 to 150 microns.

The solid diluent or carrier in the composition will generally be a non-toxic water soluble material chemically inert to the medicament and will of course be acceptable for inhalation. The carrier has an effective particle size in the range 80 to 150 microns preferably 80 to 120, especially 80 to 100 microns. Examples of solid diluents or carriers which may be used in the composition of the invention include inorganic salts, e.g. sodium chloride or calcium carbonate; organic salts, e.g. sodium tartrate or calcium lactate; organic compounds, e.g. urea, propyliodone; monosaccharides, e.g. lactose or dextrose monohydrate; disaccharides, e.g. maltose or sucrose; polysaccharides e.g. starches, dextrins or dextrans. A particularly preferred diluent or carrier is lactose, e.g. crystalline lactose.

The ratio of medicament to carrier may vary depending upon the materials used. The optimum ratio will depend upon the medicament and carrier and the method by which the composition is to be applied. We have found that the use of from 10 to 75% by weight of finely divided material to 90 to 25% by weight of carrier, preferably from 20 to 60% by weight of finely divided materials, e.g. about 25 to 60% by weight of medicament to 75 to 40% by weight of carrier, in general provides satisfactory results.

The finely divided medicament may be prepared by crystallisation, direct milling down to the desired particle size range and/or particle classification. The particulate carrier may be prepared by grinding the carrier and subsequently separating out the desired fraction by conventional methods, e.g. by air classification and sieving. The surface characteristics of individual particles of both the medicament and carrier may be modified by such conventional techniques as crystallisation, spray drying and precipitation.

The composition may be prepared from the fine and coarse ingredients by mixing the ingredients together in a mixer, e.g. a planetary mixer or a rotating blender. If desired, the surfaces of the particles of medicament and/or diluent and/or carrier may be coated with a pharmaceutically acceptable material such as stearic acid, or polymers such as polyvinyl pyrrolidone. This coating procedue may serve incidentally to give a sustained release action to the medicament.

In addition to the medicament and carrier, the composition may contain other ingredients, such as colouring matter of flavouring agents such as saccharin, which are normally present in inhalant compositions. It is, however, preferred to use the minimum of such other ingredients.

The compositions according to the invention will generally be put up in gelatine, plastic or other capsules.

There is also provided, therefore, as a further feature of the invention, a dosage unit comprising a gelatine or like capsule containing a pharmaceutical composition according to the invention.

The amount of composition contained in the capsule will, of course, depend on the desired dosage. However, the capsule suitably contains from 10 to 300, preferably from 10 to 100 mg of the composition.

The invention is illustrated, but in no way limited by the following Examples.

Example 1

Commercially available ground crystalline lactose was sieved to remove material having an effective particle size of less than 80 microns. This product was then sieved through a sieve having a mesh aperture of about 110 microns to produce lactose product with an effective size in the range 80 to 110 microns.

The medicament or other material which was intended to form a finely divided material was passed through a fluid energy mill in an air stream until the product contained at least 50% by weight of particles in the effective size range 2—6 microns as determined on a Coulter counter.

Compositions containing the desired proportions of the coarse and fine materials were mixed together in a planetary mixer and the mixture then passed through a 30 mesh sieve to remove or break up agglomerated particles.

The compositions were then put up in gelatine capsules containing about 40 mg of

the composition (capsules approximately 1/3 full) and the ease of emptying of the composition from the capsule determined. The ease of emptying was assessed by mounting a pierced capsule in the capsule holder of the powder insufflator of French Patent Specification No. 1,471,722 (which corresponds to British Patent Specification No. 1,122,284). The insufflator was then mounted in a hole in the side wall of a chamber connected to bellows. The bellows were designed to suck air through the chamber; the insufflator acting as the air inlet thereinto.

The capsule was weighed prior to mounting in the insufflator. The bellows were then operated to give seven one second sucks and the capsule reweighed to determine the amount of powder removed from the capsule. The amount of powder removed is related to the ease of fluidisation of the powder.

By way of comparison a composition containing no coarse diluent was prepared and tested. Those compositions containings the coarse carrier were all found to empty from the capsule at a satisfactory rate, whereas in the absence of the coarse diluent the emptying rates were much lower, about 15% or less, and were unpredictable.

Example 2

Compositions consisting of a mixture of 20 mg. of fine disodium cromoglycate produced by the fluid energy milling procedure described in Example 1, and 20 mg of coarse lactose of varying particle size were put up in gelatine capsules and their ease of emptying assessed by the following procedure:

A series of 20 of the powder insufflators of British Patent Specification No. 1,122,284 were mounted simultaneously in an air flow device which is adapted to reproduce one form of a human inhalation cycle. The weighed capsules were mounted in the insufflators, pierced and the insufflators were then subjected to 4 inhalation cycles and the capsules were then removed and re-weighed. The difference in weight between the capsules before and after the 4 inhalation cycles is then expressed thus:—

$$\%\ \text{emptying} = \frac{\text{Weight emptied}}{\text{Weight of contents}} \times 100$$

The results are given in Table I.

TABLE 1

	Size Ranges of Lactose in Microns		
	80—150	80—120	120—150
% emptying mean of 20 capsules	96.8%	95.5%	97.9%

WHAT WE CLAIM IS:—

1. A pharmaceutical powder composition, which comprises a mixture of a solid inhalation medicament having an effective particle size, as hereinbefore defined, in the range 0.01 to 10 microns and a solid carrier acceptable in the lungs, having an effective particle size, as hereinbefore defined, in the range of from 80 to 150 microns.

2. A composition according to Claim 1, wherein the medicament is a medicament for the alleviation of a disorder of the bronchial tract.

3. A composition according to Claim 1, wherein the medicament is an antianaphylactic agent.

4. A composition according to any one of the preceding claims, wherein the medicament is the di-sodium salt of 5,5′ - [[5,5′ - (2 - hydroxytrimethylene)dioxy]bis[4 - oxo - 4H - 1 - benzopyran - 2 - yl]] tetrazole.

5. A composition according to any one of Claims 1 to 3, wherein the medicament is sodium cromoglycate.

6. A composition according to Claim 1 or Claim 2, wherein the medicament is a bronchodilator, antibiotic, steroid, enzyme, vitamin, antihistamine, mucolytic, diagnostic agent, or analgesic.

7. A composition according to any one of the preceding claims, wherein the medicament has an effective particle size, as hereinbefore defined, in the range 1 to 10 microns.

8. A composition according to any one of the preceding claims, wherein at least 50% by weight of the medicament is in the effective particle size range 2 to 6 microns.

9. A composition according to any one of the preceding claims, wherein the carrier is a water soluble material chemically inert to the medicament.

10. A composition according to any one of the preceding claims, wherein the carrier has an effective particle size in the range 80 to 120 microns.

11. A composition according to any one of the preceding claims, whereis the carrier has an effective particle size in the range 80 to 100 microns.

12. A composition according to any one of the preceding claims, wherein the carrier is an inorganic salt, an organic salt, urea, propyliodone, a monosaccharide, a disaccharide or a polysaccharide.

13. A composition according to any one of the preceding claims, wherein the carrier is lactose.

14. A composition according to Claim 13, wherein the carrier is crystalline lactose.

15. A composition according to any one of the preceding claims comprising from 10 to 75% by weight of medicament and from 90 to 25% by weight of carrier.

16. A composition according to Claim 15 comprising from 25 to 60% by weight of medicament and 75 to 40% by weight of carrier.

17. A dosage unit comprising a capsule containing a composition according to any one of the preceding claims.

18. A dosage unit comprising from 10 to 300 mg of a composition according to any one of Claims 1 to 16.

19. A dosage unit comprising from 10 to 100 mg of a composition according to any one of Claims 1 to 16.

20. A method of preparing a composition according to any one of Claims 1 to 16 which comprises mixing the ingredients.

21. A pharmaceutical composition according to Claim 1 and substantially as hereinbefore described.

22. A pharmaceutical composition according to Claim 1 and substantially as hereinbefore described in either Example 1 or Example 2.

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